--32. The method according to claim 8, wherein the endonuclease is SceI or CRE.

33. The method according to claim 8, wherein the neurodegenerative disease is latero spinal amyotrophy (LAS).--

REMARKS

Claims 1-19 and 21-33 are pending in this application. Claim 20 has been canceled without prejudice or disclaimer. Claims 32 and 33 have been added. Support for claims 32 and 33 can be found, for example, in claim 8.

Claims 8, 15, 16, 19, 21, 24, 25, and 29-31 have been amended to remove multiple dependencies solely in an effort to reduce the filing fee associated with this application. Claim 8 was further amended to remove information that has been incorporated into new claims 32 and 33. Therefore, these amendments are not being made for any reason related to patentability, as discussed in Festo Corp. v. Shoketsu Kinzoka Kogyo Kabushiki Co., Ltd., 234 F.3d 558, 56 U.S.P.Q.2d 1865 (Fed. Cir. 2000), cert. granted, 69 U.S.L.W. 3673 (U.S. June 18, 2001) (No. 00-1543).

The specification was amended to include SEQ ID NOs. and to insert the sequence listing. These amendments do not introduce new matter into the specification.

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Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account no. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: June 29, 2001

By:_____

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APPENDIX

IN THE SPECIFICATION:

Page 7, the paragraph beginning at line 21, please replace with the following paragraph:

[FIGURE 1 shows] FIGURE 1A and FIGURE 1B show the DNA sequence and amino acid sequence of the TTC fragment cloned in pBS:TTC.

Page 19, last paragraph, beginning at line 17 and continuing through page 20, line 13:

Full length TTC DNA was generated from the genomic DNA from the *Clostridium Tetani* strain (a gift from Dr. M. Popoff, Institut Pasteur) using PCR. Three overlapping fragments were synthesized: PCR1 of 465 bp (primer 1: (SEQ ID NO:4) 5'-CCC CCC GGG CCA CCA TGG TTT TTT CAA CAC CAA TTC CAT TTT CTT ATT C-3' and primer 2: (SEQ ID NO: 5) 5'-CTA AAC CAG TAA TTT CTG-3'), PCR2 of 648 bp (primer 3: (SEQ ID NO:6) 5'-AAT TAT GGA CTT TAA AAG ATT CCG C-3' and primer 4: (SEQ ID NO: 7) 5'-GGC ATT ATA ACC TAC TCT TAG AAT-3') and PCR3 of 338 bp (primer 5: (SEQ ID NO: 8) 5'-AAT GCC TTT AAT AAT CTT GAT AGA AAT-3' and primer 6: (SEQ ID NO: 9) 5'-CCC CCC GGG CAT ATG TCA TGA ACA TAT CAA TCT GTT TAA TC-3'). The three fragments were sequentially introduced into pBluescript KS+ (Stratagene) to give pBS:TTC plasmid. The upstream primer 1 also contains an optimized eukaryotic Ribosome Binding Site (RBS) and translational initiation signals. Our TTC fragment (462 amino acids) represents the amino acids 854-1315 of tetanus holotoxin, i.e. the carboxy-terminal 451 amino acids of the heavy chain, which constitute the fragment C

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plus 11 amino acids of the heavy chain that immediately precede the amino terminus of the fragment C. The DNA sequence and amino acid sequence of the TTC fragment cloned in pBS:TTC is shown in Figure 1. The construct pBS:TTC is shown in Figure 2.

Page 20, second paragraph, beginning at line 15 through page 21, line 2:

pGEX:*lacZ* was obtained by cloning a *SmaI/XhoI lacZ* fragment from the pGNA vector (a gift from Dr. H. Le Mouellic) into pGEX 4T-2 (Pharmacia). PCR was used to convert the *lacZ* stop codon into an *NcoI* restriction site. Two primers (upstream: (SEQ ID NO: 12) 5'-CTG AAT ATC GAC GGT TTC CAT ATG-3' and downstream: (SEQ ID NO: 13) 5'-GGC AGT CTC GAG TCT AGA CCA TGG CTT TTT GAC ACC AGA C-3') were used to amplify the sequence between *NdeI* and *XhoI*, generating pGEX:*lacZ(NcoI)* from pGEX:*lacZ*. pGEX:*lacZ*-TTC was obtained by insertion of the TTC *NcoI/XhoI* fragment into pGEX:*lacZ(NcoI)*, fusing TTC immediately downstream of the *lacZ* coding region and in the same reading frame. Figure 3 shows the details of the pGEX:*lacZ*-TTC construct.

Page 21, paragraph beginning at line 4:

pBS:TTC was modified to change *NcoI* into a *BamHI* restriction site (linker (SEQ ID NO: 14) 5'-CAT GAC TGG GGA TCC CCA GT-3') at the start of the TTC DNA, to give pBS:TTC*(BamHI)* plasmid. pGEX:TTC was obtained by cloning The TTC *BamHI/SmaI* fragment from pBS:TTC*(BamHI)* into pGEX 4T-2 (Pharmacia). PCR was used to convert the TTC stop codon into an *NheI* restriction site. Two primers (upstream: (SEQ ID NO: 15) 5'-TAT GAT AAA AAT GCA TCT TTA GGA-3' and downstream: (SEQ ID NO: 16) 5'-TGG AGT CGA CGC TAG CAG GAT CAT TTG TCC

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ATC CTT C-3') were used to amplify the sequence between *NsiI* and *SmaI*, generating pGEX:TTC*(NheI)* from pGEX:TTC. The lacZ cDNA from plasmid pGNA was modified in its 5' extremity to change *SacII* into an *NheI* restriction site (linker 5'-GCT AGC GC-3'). pGEX:TTC-*lacZ* was obtained by insertion of the *lacZ NheI/XhoI* fragment into pGEX:TTC*(NheI)*, fusing *lacZ* immediately downstream of the TTC coding region and in the same reading frame. The details of the construct of pGEX:TTC-*lacZ* are shown in Figure 4.

Page 21, paragraph beginning at line 21 through page 22, line 2:

pCMV vector was obtained from pGFP-C1 (Clontech laboratories) after some modifications: GFP sequence was deleted by a [BglII/NheI] *BglII/NheI* digestion and [relegation] religation, and *SacII* in the polylinker was converted into an *AscI* restriction site (linkers 5'-GAT ATC GGC GCG CCA GC-3' (SEQ ID NO: 17) and (SEQ ID NO: 18) 5'-TGG CGC GCC GAT ATC GC-3').

Page 22, second paragraph, beginning at line 3 through line 14:

pBluescript KS+ (Stratagene) was modified to change *XhoI* into an *AscI* restriction site (linker (SEQ ID NO: 19) 5'-TCG ATG GCG CGC CA-3'), giving pBS*(AscI)* plasmid. pBS:*lacZ*-TTC was obtained by cloning a *XmaI lacZ*-TTC fragment from pGEX:*lacZ*-TTC into pBS*(AscI)*. pCMV:*lacZ*-TTC was obtained by insertion of the *lacZ*-TTC *XmnI/AscI* fragment into pCMV vector at the *XhoI* and *AscI* sites (*XhoI* and *XmnI* was eliminated with the clonage), putting the fusion downstream of the CMV promotor. Figure 8 shows the details of the construct pCMV:*lacZ*-TTC. Plasmid pCMV:*lacZ*-TTC was deposited on August 12, 1997, at the Collection Nationale de Cultures de

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Microorganisms (CNCM), Institut Pasteur, 25, Rue [de] du Docteur Roux, F-75724, Paris Cedex 15, France, under Accession No. I-1912.

IN THE CLAIMS:

8. (Amended) The method according to claim 6 [or claim 7], wherein the molecule is selected from the group consisting of protein SM, BDNF (Brain-derived neurotrophic factor), NT-3 (Neurotrophin-3), NT-4/5, GDNF (Glial cell-line-derived neurotrophic factor), IGF (Insulin-like growth factor), PNI (protease nexin I), SPI3 (Serine Protease Inhibitor protein), ICE (Interleukin-1ß converting enzyme), Bc1-2, GFP (green fluorescent protein), an [endonucleases like I-SceI or CRE] endonuclease, antibodies, or drugs specifically directed against a neurodegenerative [diseases] disease [such as latero spinal amyotrophy (LSA)].

15. (Amended) The method according to claim 12 [or 13], wherein said vector is administered into the muscle.

16. (Amended) The method according to claim 12 [or 13], wherein the molecule is a nucleotide encoding for a protein or a polypeptide linked chemically to the fragment of tetanus toxin and being transported and expressed directly in neurons.

19. (Amended) An amino acid variant fragment having the same properties as the hybrid fragment of tetanus toxin according to claim[s] 17 [or 18].

21. (Amended) A composition containing an active molecule in association with a hybrid fragment of tetanus toxin according to claim[s] 17 [or 18 or with an amino acid variant fragment according to claim 16].

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24. (Amended) A vector comprising a promoter capable of expression in muscle cells and optionally an enhancer, a nucleic acid sequence coding for the fragment of tetanus toxin according to claim[s] 17, [or 18 or with an amino acid variant fragment according to claim 19] wherein the nucleic acid sequence is associated with a polynucleotide coding for a protein or a polypeptide.

25. (Amended) A method of treatment of a patient or an animal affected with CNS or spinal cord disease, which comprises delivering a composition according to claim[s] 21[, 22, or 23] to the patient or animal in an amount effective for treatment of the CNS or spinal cord disease.

29. (Amended) The method according to claim 27, [or 28] wherein the molecule is a nucleotide encoding for a protein or a polypeptide linked chemically to the fragment of tetanus toxin and being expressed directly in neurons.

30. (Amended) The method according to claim 27, [or 28] wherein the molecule is a nucleotide encoding for a protein or a polypeptide linked chemically to the fragment of tetanus toxin and being expressed directly in neurons.

31. (Amended) A cell or vector comprising a promoter capable of expression in neuronal cells or precursors of neuronal cells and optionally an enhancer, a nucleic acid sequence coding for the fragment of tetanus toxin according to claim[s] 17, [or 18 or with an amino acid variant fragment according to claim 19] wherein the nucleic acid sequence is associated with a polynucleotide coding for a protein or a polypeptide.

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